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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/751,299	12/28/2000	Mark Madden	DIVER1440-2	8629

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EXAMINER	
KAM, CHIH MIN	
ART UNIT	**PAPER NUMBER**
1656	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/751,299	MADDEN ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,32,36,37,44,49,50,52-66 and 68-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *31,32,49 and 66* is/are allowed.

6)☒ Claim(s) *36,37,44,50,52-65 and 68-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 31, 32, 36, 37, 44, 49, 50, 52-66 and 68-80 are pending.

Applicants' amendment filed November 14, 2006 is acknowledged. Applicants' response has been fully considered. Claims 36, 44, 50, 66, 68, 69, 71-74 and 78 have been amended, and claim 67 has been cancelled. Therefore, claims 31, 32, 36, 37, 44, 49, 50, 52-66 and 68-80 are examined.

Withdrawn Claim Rejections -- 35 USC § 112

2. The previous rejection of claims 66-67 under 35 U.S.C. 112, first paragraph, scope of enablement, is withdrawn in view of applicant's amendment to the claims, applicants' cancellation to the claim, and applicant's response at page 17 in the amendment filed November 14, 2006.

3. The previous rejection of claims 66 and 72-76 under 35 U.S.C. 112, first paragraph, written description, is withdrawn in view of applicant's amendment to the claims, and applicant's response at page 17 in the amendment filed November 14, 2006.

4. The previous rejection of claims 44, 66-68, 71, 72 and 77-80 under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicant's amendment to the claims, applicants' cancellation to the claim, and applicant's response at page 17 in the amendment filed November 14, 2006.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 44, 50 and 68-80 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of stereoselectively producing an alpha-substituted carboxylic acid having the structure of $C(R_1)(R_2)(E)(COOH)$, where R_1, R_2 and E is defined in the claim 44, using a polypeptide of nitrilase, wherein the nitrilase consists of SEQ ID NO:2 or SEQ ID NO:4, or, is encoded by a nucleic acid consisting of SEQ ID NO:1 or SEQ ID NO:3, does not reasonably provide enablement for a method of stereoselectively producing an alpha-substituted carboxylic acid having the structure of $C(R_1)(R_2)(E)(COOH)$, where R_1, R_2 and E is defined in the claim 44, using a polypeptide of nitrilase, wherein the nitrilase has an amino acid sequence having at least 90% (or at least 85% for claims 78-80) sequence identity to the sequence of SEQ ID NO:2 or SEQ ID NO:4 and retains the biological activity of SEQ ID NO:2 or SEQ ID NO:4, or, is encoded by a nucleic acid having at least 90% sequence identity to the sequence of SEQ ID NO:1 or SEQ ID NO:3 and retains the same enzyme activity as the enzyme encoded by the sequence of SEQ ID NO:1 or SEQ ID NO:3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 44, 50 and 68-80 encompass a method of stereoselectively producing an alpha-substituted carboxylic acid using a polypeptide of nitrilase, wherein the nitrilase has an amino acid sequence having at least 90% (or at least 85%) sequence identity to the sequence of SEQ ID NO:2 or SEQ ID NO:4 and retains the biological activity of SEQ ID NO:2 or SEQ ID NO:4, or, is encoded by a nucleic acid having at least 90% sequence identity to the sequence of SEQ ID

NO:1 or SEQ ID NO:3 and retains the same enzyme activity as the enzyme encoded by the sequence of SEQ ID NO:1 or SEQ ID NO:3. The specification, however, only discloses cursory conclusions without data supporting the findings, which state that the present invention provides methods for producing enantiomerically pure α-substituted carboxylic acids, such as α-amino acids and α-hydroxy acids, the methods including combining an aldehyde or ketone with a cyanide and an ammonia-containing compound or an ammonium salt, in the presence of a nitrilase which stereoselectively hydrolyzes the amino nitrile or cyanohydrin intermediate, under conditions sufficient to produce the carboxylic acid, wherein the nitrilase has an amino acid sequence of SEQ ID NO:2 or SEQ ID NO:4 or sequences having at least 70% identity thereto and having nitrilase activity (pages 2-3). There are no indicia that the present application enables the full scope in view of the claimed method using a nitrilase related to SEQ ID NO:2 or SEQ ID NO:4 as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance to enable the full scope of the claims. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence or presence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the functional amino acid sequences having at least 90% or 85% sequence identity to the sequence of SEQ ID NO:2 or SEQ ID NO:4, being encoded by a nucleic acid having at least 90%

sequence identity to the sequence of SEQ ID NO:1 or SEQ ID NO:3, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

Example 1 shows using the nitrilase of SEQ ID NO:2 or SEQ ID NO:4 to stereoselectively produce (S)-phenylglycine from phenylglycineonitrile (or benzaldehyde, KCN and NH_4Cl). However, there are no examples indicating the use of amino acid sequences related to SEQ ID NO:2 or 4, amino acid sequences encoded by nucleotide sequences having at least 90% sequence identity to the sequence of SEQ ID NO:1 or SEQ ID NO:3 as nitrilase in the claimed methods.

(3). The state of the prior art and relative skill of those in the art:

The related art (e.g., the references shown as Exhibits B-D in the amendment filed October 31, 2005) teach the sequences of several nitrilase, however, these sequences are not the same as the sequence of SEQ ID NO:2 or 4. Furthermore, there is no description regarding the sequences for variants of nitrilase peptides. Since the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide teachings on the identification of the sequences of various nitrilase peptides that are active in stereoselectively producing an alpha-substituted carboxylic acid.

(4). Predictability or unpredictability of the art:

The claims are directed to a method of stereoselectively producing an alpha-substituted carboxylic acid using a polypeptide of nitrilase, wherein the nitrilase has an amino acid sequence having at least 90% or 85% sequence identity to the sequence of SEQ ID NO:2 or SEQ ID NO:4, is encoded by a nucleic acid having at least 90% sequence identity to the sequence of SEQ ID

NO:1 or SEQ ID NO:3. While the specification indicates the polypeptide or nucleic acid sequences of nitrilase having sequence identities at least about 90% to SEQ ID NO: 2 or 4, or SEQ ID NO: 1 or 3, respectively (page 11, lines 20-30; page 42, lines 5-23), it does not identify any of the peptide variants, nor indicates the structure and function relationship for the variants. Thus, the amino sequence of a functional nitrilase peptide is unpredictable.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of stereoselectively producing an alpha-substituted carboxylic acid using a polypeptide of nitrilase related to SEQ ID NO:2 or 4. While the specification indicates using the nitrilase of SEQ ID NO:2 or SEQ ID NO:4 to stereoselectively produce (S)-phenylglycine from phenylglycineonitrile (or benzaldehyde, KCN and NH_4Cl; Example 1), the specification does not describe the use of amino acid sequences related to SEQ ID NO:2 or 4 (e.g., sequences having at least 90% sequence identity to the sequence of SEQ ID NO:2 or 4), the amino acid sequences encoded by nucleotide sequences having at least 90% sequence identity to the sequence of SEQ ID NO:1 or SEQ ID NO:3 as nitrilase in the claimed methods. Moreover, there are no working examples indicating the claimed methods associated with variants. Since the specification does not provide sufficient teachings on the make/use of the peptide variants of nitrilase in the claimed methods, it is necessary to have additional guidance and to carry out undue experimentation to identify active nitrilase polypeptides in the claimed methods and to assess the effects of these nitrilase polypeptide.

(6). Nature of the Invention

The scope of the claims encompasses a method of stereoselectively producing an alpha-substituted carboxylic acid using a polypeptide of nitrilase related to SEQ ID NO:2 or 4, but the specification does not demonstrate the make/use of various nitrilase peptide variants in the claimed method. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working examples do not demonstrate the claimed methods associated with variants, the sequences of active nitrilase peotides are unpredictable, and the teaching in the specification is limited, therefore, it is necessary to have additional guidance and to carry out undue experimentation to make/use the active nitrilase peptides in the claimed methods.

Response to Arguments

Applicants indicate that the specification enabled the skilled artisan at the time of the invention to make and use, and in particular, to identify or screen for, the claimed genus of nitrilases and nitrilase-encoding polynucleotides without undue experimentation and have provided evidence and expert declaration to support this argument (see, e.g., Applicants' response of July 17, 2003, pages 30 to 32, including Dr. Jennifer Chaplin's expert declaration). Claims 44 and 50 as amended encompass genera of amino acid sequences (90% versus 80% sequence identity to SEQ ID NO:2 or 4) and nucleic acids (90% versus 80% sequence identity to SEQ ID NO:1 or 3) progressively smaller in scope than the embodiments previously indicated in the claimed invention. Applicants also indicate the state of the art at the time of the invention and the level of skill of the person of ordinary skill in the art, e.g., screening enzymes, and nucleic acids encoding enzymes, for nitrilase activity such that the enzyme produces an alpha-substituted carboxylic acid, was very high (see Declaration of Dr. DeSantis submitted on April

11, 2005). As analogous to In re Wands and as declared by Dr. Jennifer Ann Chaplin, using the teaching of the specification and other protocols known in the art at the time of the invention one skilled in the art could have successfully practiced the methods of the invention without undue experimentation, including identifying enzymes for used in the claimed methods without specific guidance as to which residues to change, or not change. Applicants have run a routine, simple sequence alignment comparison of known nitrilase sequences with exemplary sequences of the invention to identify regions of identity and dissimilarity between nitrilases as guidance as to which residue could, or could not, be modified. Accordingly, the specification and the art provided sufficient guidance to the skilled artisan to reasonably enable him or her how to make and use the genera of nitrilase sequences of the invention without undue experimentation (see pages 15-17 of the response).

Applicants' response has been considered. However, the arguments are not fully persuasive because of the following reasons. The specification only describes the polyeptides of SEQ ID NOs: 2 and 4 as nitrilases and their activity on phenylglycinonitrile (see Example 1). There is no description on the structure and function relationship in the nitrilase peptide variants of SEQ ID NOs: 2 and 4, and how their sequences reflect their nitrilase activity. Although several nitrilase sequences were known at the time of filing of the instant application, these sequences are different from the sequence of SEQ ID NO:2 or 4. Furthermore, the prior art is relatively silent on the generic structure of nitrilases. Thus, the ability to vary the sequences disclosed and maintain nitrilase activity, in particular stereoselective nitrilase activity, is unpredictable. Furthermore, while methods to produce variants of a known sequence, such as site-specific mutagenesis, random mutagenesis, etc., are well known to the skilled artisan,

producing variants useful as nitrilase activity requires that one of ordinary skill in the art know or be provided with guidance for the selection of which, of the infinite number of variants, have the activity. Without such guidance, one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. Guo *et al.* (PNAS 101, 9205-9210 (2004)) teach that the percentage of random single-substitution mutations, which inactivate a protein, using a protein 3-methyladenine DNA glycosylase as a model, is 34% and that this number is consistent with other studies in other proteins (see page 9206, paragraph 4). Guo *et al.* further show that the percentage of active mutants for multiple mutations appears to be exponentially related to this by the simple formula $(.66)^x$ X 100% where x is the number of mutations introduced (see Table 1). Applying this estimate to the protein recited in the instant application, 90% identity allows up to 34 mutations within 337 or 346 amino acids of SEQ ID NO: 2 or 4, thus, only $(.66)^{34}$ X 100% or 7.3×10^{-5} % of random mutants having 90% identity would be active. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification. Therefore, the instant claims are not enabled to the full extent of their scope.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 36, 37, 50, 52-65, 69 and 70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 36, 37 and 52-65 are indefinite because the claim recites a method for stereoselectively producing an alpha-amino acid by contacting an aldehyde or ketone with a cyanide-containing compound and ammonia to produce amino nitrile, which would be hydrolyzed by nitrilase to produce alpha-substituted amino acid, however it also recites E being OH in the structure of $C(R_1)(R_2)(E)(COOH)$, which is not an alpha-amino acid. Claims 37 and 52-65 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

8. Claims 50, 69 and 70 are indefinite because of the use of the term "the nucleic acid encodes an enzyme that retains the same enzymatic activity as the enzyme encoded by the nucleic acid sequence from which it varies". The term cited renders the claim indefinite, it is not clear what the first nucleic acid, the second nucleic acid, or "it" refers to, does it refer to a nucleic acid having at least 90% sequence identity or the nucleotide sequence of SEQ ID NO:1 or 3. Claims 69 and 70 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

Conclusion

9. Claims 36, 37, 44, 50, 52-65 and 68-80 are rejected; it appears claims 31, 32, 49 and 66 are free of art.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

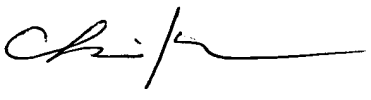
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Bragdon can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Primary Patent Examiner



CHIH-MIN KAM
PRIMARY EXAMINER

CMK
January 31, 2007